REMARKS/ARGUMENTS

All amendments are fully supported by the specification as originally filed and do not add new matter. All amendments and cancellations were made without prejudice or disclaimer. Applicants expressly reserve the right to pursue any deleted subject matter in one or more continuing applications.

Rejection Maintained Under 35 U.S.C. §103

Claims 1-3, 8-16, and 32 have been rejected as allegedly being unpatentable over WO 01/15730, in view of WO 98/02540 and Feldman et al., Dermatol Online J. 6(1):4, September 2000.

This rejection has been maintained from the previous Office Action dated May 31, 2006, and is supported by essentially repeating the earlier assertions.

The Examiner's Response to Applicants' Arguments

In addressing Applicants' arguments submitted in response to the previous similar rejection, the Examiner makes the following statements:

(1) *Hindsight reasoning*: Citing In re McLaughlin, 170 USPQ 209 (CCPA 1971), the Examiner stated: "[I]t must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper." (Office Action, page 5, first full paragraph)

"[I]t is well known to one of ordinary skill in the immunology art at the time the invention was filed that ErbB2 plays a role in psoriasis (see WO 98/02540 publication page 35, line 11, homodimer, abstract, in particular)." It was also known that "ErbBs plays a role in a benign hyperproliferative epithelia, inflammatory angiogenic immunological disorders [sic] (see WO 01/15730 publication, page 14, lines 9-14, page 30, lines 31-38, in particular.)" The success reported in WO 01/15730 in treating benign hyperproliferative epithelial, inflammatory angiogenic immunological disorders using ErbB2 antagonists "such as antibody that binds to ErbB2 in the face of having to solve a similar problem would have led one of ordinary skill in

the art at the time the invention was made to combine the references to solve a well known problem in the art." (Office Action, passage bridging pages 5 and 6).

(2) *Reasonable expectation of success*: In addressing Applicants' arguments that psoriasis is a chronic disease that is difficult to treat and the present invention has only been created by demonstrating the ability of the antibodies herein to block signaling through the MAP kinase pathway, the activation of which was, in turn, known to be responsible for epidermal hyperpoliferation in psoriasis, the Examiner notes that "none of the claims recite antibody that binds to ErbB2 [and] block ErbB2 signaling through the MAP kinase pathway." The Examiner further notes hat "there is no evidence in the specification as filed that treating a human patient with psoriasis with any antibody which binds ErbB2 such as antibody that binds to the same epitope in the extracellular domain of ErbB2 as that bound by monoclonal antibody 2C4 or humanized 2C4 or monoclonal antibody 2C4 inhibits MAP kinase pathway in human." (Office Action, page 6, first full paragraph)

Applicants continue to disagree, and respectfully traverse the rejection.

The finding of obviousness is incorrect and should be withdrawn

Obviousness inquiry is controlled by the factors articulated by the Supreme Court in *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1 (1966), including: 1) the scope and content of the prior art; 2) the differences between the prior art and the claims; 3) the level of ordinary skill in the pertinent art; and 4) objective evidence of nonobviousness. In addition, a long line of Federal Circuit decisions has established that a patent claim is only proved obvious if the prior art, the problem's nature, or the knowledge of a person of ordinary skill in the art provides some motivation or suggestion to combine the prior art teachings (the "teaching, suggestion, or motivation" or "TSM" test).

While the Supreme Court has recently rejected a rigid application of the TSM test, it stated that the Graham Deere factors still control an obviousness inquiry. See KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. at 1727. Moreover, the Court indicated that there is "no necessary inconsistency between the idea underlying the TSM test and the Graham analysis." KSR, 127 S. Ct at 1731. The Court specifically acknowledged the importance of identifying "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does" in an obviousness determination. Id. As long as the

test is not applied as a "rigid and mandatory" formula, that test can provide "helpful insight" to an obviousness inquiry. Id. Applying these principles, the Federal Circuit has recently confirmed that in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish *prima facie* obviousness of a new claimed compound. See Takeda Chemical Indus. v. Alphapharm Pty., Ltd., No. 06-1329, slip op (Fed. Cir. June 28, 2007), at 9-10.

WO 01/157030 was cited for its teaching of the treatment of various non-malignant conditions, including inflammatory and immunologic conditions, using ErbB2 antibodies. WO 98/02540 was cited for allegedly teaching the use of heterodimeric immunoadhesins, including the extracellular domains of at least two different ErbB receptors, e.g. ErbB1/ErbB3, ErbB2/ErbB4 or ErbB3/ErbB4, to treat psoriasis. In fact, WO 98/02540 teaches the use of certain chimeric ErbB heteromultimer adhesins as being useful as competitive antagonists of a neuregulin, which can be used to treat

> *"benign or malignant tumors (e.g. renal, liver, kidney, bladder, breast, gastric, ovarian, colorectal, prostate, pancreatic, ling, vulval, thyroid, hepatic carcinomas; sarcomas; glioblastomas; and various head and neck tumors); leukemias and lymphoid malignancies; other disorders such as neuronal, glial, astrocytal, hypothalamic and other glandular, macrophagal, epithelial, stromal and blastocoelic disorders; inflammatory, angiogenic and immunologic disorders; psoriasis and scar tissue formation. HRG antagonists may also be used to reverse resistance of tumor cells to the immune-response, to inhibit pathological angiogenesis and to stimulate the immune system."* (Page 25, lines 1-10, emphasis added).

The reference further teaches that

> *"It may be desirable to treat the mammal with a HRG antagonist, such as an ErbB-Ig chimeric heteroadhesin, particularly where excessive levels of HRG are present and/or excessive activation of ErbB receptors by HRG is occurring in the mammal. Exemplary conditions or disorders to be treated with a HRG antagonist include benign or malignant tumors (e.g. renal, liver, kidney, bladder, breast, gastric, ovarian, colorectal, prostate, pancreatic, ling, vulval, thyroid, hepatic carcinomas; sarcomas; glioblastomas; and various head and neck tumors); leukemias and lymphoid malignancies; other disorders such as neuronal, glial, astrocytal, hypothalamic and other glandular, macrophagal, epithelial, stromal and blastocoelic disorders; inflammatory, angiogenic and immunologic disorders; psoriasis and scar tissue formation. HRG antagonists may also be used to reverse resistance of tumor cells to the immune-response, to inhibit pathological angiogenesis and to stimulate the immune system.* (Page 25, lines 1-10)

and the anti-ErbB chimeric heteroadhesins, as HRG antagonists,

> *"may be administered to patients suffering from neurologic diseases or disorders characterized by excessive production of HRG and/or excessive ErbB receptor activation by HRG. An anti-ErbB chimeric heteroadhesin antagonist antibody may be used in the prevention of aberrant regeneration of sensory neurons such as may occur post-operatively, or in the selective ablation of sensory neurons, for example, in the treatment of chronic pain syndromes."* (Page 25, lines 13-16)

Thus, contrary to the Examiner's assertion, the teaching of WO 98/02540, when read without the benefit of the teaching of the invention claimed in the present application is not that "a method of treating psoriasis by administering to the mammal with an agent [sic] that blocks the ErbB2 ligand from binding to its receptor" (Office Action, page 3, second full paragraph), rather that chimeric ErbB heteromultimer adhesins are useful for the treatment of a long list of diseases and conditions, including, apart from psoriasis, a variety of malignancies, neuronal, glial, astrocytal, hypothalamic and other glandular, macrophagal, epithelial, stromal and blastocoelic disorders; inflammatory, angiogenic and immunologic diseases.

In order to arrive at the invention claimed in the present application, the skilled artisan (1) would be required to select the once mentioned psoriasis of the long list of diseases targeted by the heteromultimer adhesins of WO 98/02540, and (2) must assume that the anti-ErbB2 antibodies of WO 01/157030 will behave the same way as the ErbB heteromultimer adhesins of WO 98/02540. Without the benefit of the disclosure of the present application, there is no reasonable basis for either assumption.

There is nothing that would make a person skilled in the art select psoriasis out of the numerous diseases and conditions listed in WO 98/02540 than the teaching of the present invention. And there is no reason why one of ordinary skill in the art would substitute ErbB2 antibodies for the heterodimeric adhesins of WO 98/02540 and assume that the two different classes of compounds would be functionally equivalent. The Examiner cites WO 98/02540 (page 35, line 11, homodimer, abstract, in particular) as allegedly establishing that "it is well known to one of ordinary skill in the immunology art at the time the invention was filed that ErbB2 plays a role in psoriasis." (Office Action, passage bridging pages 5 and 6). WO 98/02540 teaches no such thing. Page 35, line 11 is the first line of Example 1, which describes the construction, isolation and biochemical characterization of the ErbB2-IgG, ErbB2-IgG, and

ErbB4-IgG chimeric amino acid sequences and the resultant chimeric heteromultimers, which are illustrated in the Figure accompanying the Abstract. The Abstract itself states:

> *"The chimeric ErbB heteromultimer adhesins of the present invention are useful as competitive antagonists or agonists of a neuregulin for the treatment of diseases such as various cancers."*

Elsewhere, it is explained that the heteromultimer adhesins have one or more of the following properties: (a) the ability to compete with a natural heteromultimeric receptor for binding to a neuregulin, such as heregulin; (b) the ability to form ErbB2-lgG/ErbB3-lgG and/or ErbB2-IgG/ErbB4-IgG complexes; and (c) the ability to inhibit activation of a natural heteromultimeric receptor by depleting heregulin from the environment of the natural receptor, thereby inhibiting proliferation of cells that express the ErbB2 and ErbB3 receptor and/or the ErbB2 and ErbB4 receptor. (See, e.g. page 22, lines 29-34)

Thus, the teaching of WO 98/02540 is not that ErbB2 plays a role in psoriasis, rather that neuregulins, such as heregulin, is involved in psoriasis, along with a variety of other diseases.

Accordingly, there is no basis for combining the teaching of WO 98/02540 with the teaching of WO 01/15730, and even when the teachings are combined, there is no reasonable expectation that the antibodies of the present invention would be effective in the treatment of psoriasis. Indeed, there is no doubt that the Examiner has used the disclosure of the present application to pick and choose a selected portion of the disclosure of WO 98/02540, which was then combined with the disclosure of WO 01/157030 in an attempt to recreate the claimed invention. The Examiner's assertion that "any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning," is no excuse for an improper hindsight reconstruction of a claimed invention, which, instead of looking at the prior art as a whole, picks and chooses teaching that appears to support a finding of obviousness, while completely disregards others.

As explained in Applicants' response to the previous Office Action of identical content, psoriasis is a chronic diseases that is difficult to treat. A reasonable expectation that such treatment is likely to work by following the methods of the present invention has only been created by demonstrating the ability of the antibodies herein to block signaling through the MAP kinase pathway, the activation of which was, in turn, known to be responsible for epidermal hyperproliferation in psoriasis. This feature is now recited in the claims.

The third reference cited, Feldman et al. was cited for its teaching of treating psoriasis with immunosuppressive agents or a combination thereof. This reference adds nothing that would make up for the deficiencies of the first two references.

For all the reasons discussed above, Applicants maintain that a *prima facie* case of obviousness has not been established, and the present rejection should be withdrawn.

New Objection and Rejections

(1) Claim 32 has been objected to due to the misspelling pf the name "Etanecerpt." The cancellation of claim 32, which was done without prejudice and without acquiescing to the present rejection, moots its rejection.

(2) Claims 15 and 32 have been rejected under 35 U.S.C. §112, first paragraph for alleged lack of enablement. Since claims 15 and 32 are canceled, their rejection is moot. It is emphasized, however, that the claims have been canceled with the sole purpose of expediting prosecution, and should not be construed as an acquiescence in the rejection, or the Examiner's reasoning underlying the rejection.

(3) Claims 15 and 32 have been rejected under 35 U.S.C. §112, first paragraph for allegedly failing to comply with the written description requirement. Applicants disagree, but in order to advance prosecution, have decided to cancel these claims, which moots their rejection.

(4) Claims 2 and 32 have been rejected under 35 U.S.C. §112, second paragraph as allegedly being "indefinite" in its recitation of an "ErbB receptor," since claim 1, from which claim 2 depends recited binding to an "ErbB2 receptor." The current amendment of claim 2 is believed to obviate this rejection.

(5) Claims 1-3, 8-16, and 32 were rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over WO 01/15730 in view of U.S. Patent No. 5,650,415 (the '415 patent).

WO 01/15730 was cited as in the earlier rejection, for its teaching of the treatment of "a benign hyperproliferative epithelial, inflammatory angiogenic immunological disorder" by administering an antibody that binds ErbB2. According to the rejection, the "claimed invention differs from the teachings of the reference only in that the method [is] for therapeutic treatment of psoriasis instead of benign hyperproliferative epithelial, inflammatory angiogenic immunological disorders." (Office Action, page 14, second full paragraph)

The '415 patent is cited for allegedly teaching that "tyrosine kinase includes HER family such as EGFR, HER2, HER3 and HER4, and many of these kinases have been found to be

involved in cellular signaling pathways leading to pathogenic conditions such as cancer, psoriasis, and hyperimmune response, etc (see col. 1, lines 24-42, in particular)." (Office Action, page 14, third full paragraph) The '415 patent is further cited for allegedly teaching that various tyrosine kinase inhibitors are useful for treating cell proliferative disorders involving HER2, such as cancer and psoriasis.

From this, the Examiner concludes that "it would have been obvious to one of ordinary skill in the art at the time the invention was made to treat psoriasis by either substitution and/or combining the tyrosine kinase inhibitor that inhibit [sic] HER2 cellular signaling pathways as taught by the '415 patent for the antibody or binding fragment thereof which binds to ErbB2 that is useful for treating benign hyperproliferative epithelial, inflammatory angiogenic immunological disorders as taught by the WO 01/15730 application." (Office Action, passage bridging pages 14 and 15)

The Examiner asserts that there is a motivation to combine with the expectation of success, since "many HER2 family of tyrosine kinases [sic] have been found to be involved in cellular signaling pathways leading to pathogenic conditions such as cancer, psoriasis, and hyperimmune response, etc. . . . and tyrosine kinase inhibitor inhibits cellular tyrosine kinase signaling in psoriasis." (Office Action, page 15, first full paragraph).

Applicants disagree and vigorously traverse the rejection.

The '415 patent provides a class of small molecule quinoline compounds, characterized as tyrosine kinase inhibitors, for use in methods of inhibiting cell proliferation or differentiation.

As the '415 patent explains in the Background of the Invention section,

> *There are 19 known families of receptor tyrosine kinases including the Her family (EGFR, Her 2, Her 3, Her 4), the insulin receptor family (insulin receptor, IGF-1R, insulin-related receptor), the PDGF receptor family (PDGF-R-α and -β, CSF-1 R, kit, Flk2), the Flk family (Flk-1, Flt-1, Flk-4), the FGF-receptor family (FGF-Rs 1 through 4), the Met family (Met, Ron), etc. There are 11 known families of non-receptor type tyrosine kinases including the Src family (src, yes, fyn, lyn, lck, blk, Hck, Fgr, yrk), Abl family (Abl, Arg), Zap 70 family (Zap 70, Syk) and Jak family (Jak 1, Jak 2, Tyk 2, Jak 3). Many of these tyrosine kinases have been found to be involved in cellular signalling pathways leading to pathogenic conditions such as cancer, psoriasis, hyperimmune response, etc."*

In view of the size and diversity of the tyrosine kinase receptor families, it is not surprising that the patent lists different target disorders not only for each individual family, but also members within the same family. Thus, of the tyrosine kinases that form the HER family,

HER2 driven disorders are described as being characterized by inappropriate or over-activity of HER2, which can be correlated with cell proliferative disorders, in particular, various cancers, such as breast cancer. Psoriasis is not mentioned as a disorder that would be associated with the HER2 receptor, and there is no teaching or suggestion that psoriasis would be associated with inappropriate or over-activity of HER2.

Indeed, of the HER family of tyrosine kinases, psoriasis is listed only among the EGFR disorders. In view of this clear distinction between the HER2 driven disorders and EGFR disorders, one of ordinary skill in the pertinent art would not expect inhibitors of the HER2 receptor, such as anti-HER2 antibodies, be effective in the treatment of psoriasis. Accordingly, contrary to the Examiner's assertion, one or ordinary skill in the art would have no motivation to combine the teaching of the '415 patent with the teaching of WO 01/15730 directed to HER2 (ErbB2) antibodies, and even if the combination were proper, it would not create a reasonable expectation that the HER2 (ErbB2) antibodies could treat psoriasis.

Just as in the obviousness rejection maintained from the previous Office Action, the Examiner uses the teaching of the present application engaging in impermissible hindsight reconstruction of the invention claimed in the present application. As hindsight is abhorrent to obviousness considerations, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

(6) Claims 1 and 15 have been rejected under 35 U.S.C. §03(a) as allegedly being obvious over WO 01/15730 in view of U.S. Patent No. 5,650,415 (the '415 patent) and U.S. Patent No. 5,783,186 (the '186 patent).

The first two references have been cited as in the previous rejection. The '186 patent is cited for its teaching that anti-HER2 antibodies induce apoptosis of cells expressing the HER2 receptor and tag HER2 overexpressing cells for elimination by the host immune system.

From the combination of the there references, the Examiner concludes that "it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the Her2 (ErbB2) antibody that induces apoptosis as taught by the '186 patent with any one of the antibody [sic] that binds ErbB2 as taught by the WO 01/15730 publication for treating psoriasis by inhibiting the HER family such as EGFR, HER2, HER3 and HER4 kinases that have been found to be involved in pathogenic conditions such as cancer, psoriasis as taught by the '415 patent." (Office Action, passage bridging pages 16 and 17.)

Claim 15 has been canceled. The rejection of claim 1 is respectfully traversed.

In response to the previous rejection, Applicants have shown that WO 01/15730 and the '415 patent cannot be properly combined, and even if the combination were proper, the combined disclosures of the two documents do not create a reasonable expectation of success for the treatment of psoriasis with the antibodies of the present invention that bind ErbB2, and block ErbB2 signaling through the MAP kinase pathway. The '186 patent, which is even farther removed from the invention claimed in the present application does not add anything that could make up for the deficiencies of the two primary references, and therefore, does not support the present rejection, which is believed to be misplaced and should be withdrawn.

(7) Claims 1 and 32 have been rejected under 35 U.S.C. §103(a) as allegedly obvious over WO 01/15730 in view of U.S. Patent No. 5,650,415 (the '415 patent) and Feldman et al., Dermatol Online J. 6(1), 2000.

WO 01/15730 and the '415 patent have been applied as in the previous rejections. Feldman et al. is cited as in the obviousness rejection maintained from the previous Office Action, namely for teaching a method of treating psoriasis using various immunosuppressive agents or their combinations.

The cancellation of claim 32 moots its rejection. The rejection of claim 1 is respectfully traversed.

In response to the previous rejection, Applicants have shown that WO 01/15730 and the '415 patent cannot be properly combined, and even if the combination were proper, the combined disclosures of the two documents do not create a reasonable expectation of success for the treatment of psoriasis with the antibodies of the present invention that bind ErbB2, and block ErbB2 signaling through the MAP kinase pathway. The Feldman et al. paper, which is even farther removed from the invention claimed in the present application does not add anything that could make up for the deficiencies of the two primary references, and therefore, does not support the present rejection, which is believed to be misplaced and should be withdrawn.

All claims pending in this application are believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **39766-0205**).

Respectfully submitted,

Date: September 11, 2007

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